REMARKS

Claims 1-30 are presently pending in the instant Application. In the instant Amendment, Claim 6 has been amended to correct minor formal errors made in amending Claim 6 in the previous Amendment.

The Invention is Unobvious

Claims 1-7 and 9 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent 5,314,506 (the '506 patent). The Examiner has asserted that instant Claims 19, 29 and 30 recite particles of sizes between 1 and 10. It is the Examiner's belief that the '506 patent teaches crystals having a diameter equal to less than 20 microns. In support of this assertion, the Examiner has referred to Claim 5 of the '506 patent. Hence, it is the Examiner's position that Claims 1-7, 9, 19-25, 27, and 29-40 are obvious in light of the teachings of the '506 patent.

Furthermore, in response to arguments previously made, the Examiner has asserted that: (a) the '506 patent is in the same field of endeavor as the instant Invention, and is directed towards solving the same problem as that of the instant Invention, i.e., producing particles of drugs or medicaments having high bioavailability and short dissolution times by avoiding milling and introducing jet processes; (b) Applicants agree the '506 patent recognizes the volume flow of feed and anti-solvent as an important factor in producing crystals having desired particle; and (c) Applicants have admitted that the '506 patent suggests wide ratios of the volume flows. Thus, it is the Examiner's position that, absent any criticality of the instant claimed velocity, it would have been within the scope of a skilled artisan to optimize the volume flows of the solvent and anti-solvents, and their ratios from the prior art teachings of wide ratios so as to achieve the desired particle sizes because, in the Examiner's opinion, the '506 patent suggests using higher velocities.

In addition, the Examiner disagrees with Applicants' position that the teachings of the '506 patent significantly differ from the instant Invention in controlling the velocity of jet streams to remove substantially cyclic variations resulting in higher quality of crystal. In particular, the Examiner believes the data Applicants cited on page 10 of the instant Specification to demonstrate that controlling the velocity of streams to remove cyclic variations only included velocities of 30 m/s or higher, and did not include the lower velocities of the prior art (as taught by the '506 patent). Accordingly, it is the Examiner's position a meaningful comparison cannot be made between the flow rates (within and outside the claimed scope), and the cyclic variations and the quality of crystals. Furthermore, the Examiner has asserted the instant Claim does not clearly recite the means for controlling the variations. Hence, it is the Examiner's position that the limitation "velocity of each step is controlled" recited in the rejected Claims does not distinguish the instant Invention from the method taught by the '506 patent.

This rejection is respectfully traversed. As explained earlier to the Examiner, significant differences exist between the teachings of the '506 patent and the instant Invention that clearly would not be obvious to one of ordinary skill in the art in light of the teachings of the '506 patent alone, or in combination with other references the Examiner has cited. For example, the instant Invention clearly teaches that the ratio of the volume flow of anti-solvent to volume flow of medicament solution exceeds 2:1. Indeed, it is made clear at page 8, lines 10-13 of the instant Application that:

> As described above ***an excess of anti-solvent is needed and the ratio of the flow rate of anti-solvent to medicament solution must be greater than 2:1***, preferably greater than 10:1, and even more preferably 15:1 and 30:1 (emphasis added).

The Examiner has cited the examples of the '506 patent to support the assertion that the '506 patent teaches that much greater amounts of anti-solvent are used as compared to the

amount of medicament solution used (paper No. 10, page 3). Yet, taken as a whole, the '506 patent contains no such teaching. In particular, example 2 of the '506 patent teaches "the flow rate from ***each*** jet was 1.1 liter/min (emphasis added)." Similarly, Examples 6 and 7 of the '506 patent teach the volume flow rate for the anti-solvent and medicament solution are equal (see col. 6, lines 9-29 and lines 43-65, respectively). Example 5 even teaches the use of a ***greater*** volume of feed solution than anti-solvent (see col. 9, lines 60-67). Claim 16 of the '506 patent does teach the use of a volumetric ratio of 41:59 for feed solution to anti-solvent in a process for crystallizing simvastatin, which is greater than 1 (but hardly 2:1). Yet, col. 8, lines 9-14 of the '506 patent explains:

> .... In this case, the composition of the impinging jet streams is 50:50 MeOH:H_2O, and the composition in the age tank is brought to 41:59 MeOH:H_2O by a separate, additional water injection ***(not through the impinging jet)*** directly into the stirred vessel (emphasis added)....

Furthermore, col. 6, lines 63-68 through to col. 7, lines 1-2 of the '506 patent make clear that, "....For example, if a 4:1 volumetric ratio of ***feed solution to anti-solvent*** is desired, the entry tube delivering solution should be twice the diameter of the entry tube delivering anti-solvent (emphasis added)."

In light of wide range of volumetric ratios used, the '506 patent, as a whole, clearly ***does not*** teach or suggest that the volume ratio of anti-solvent to medicament solution always be 2:1 or greater during the impingement of the jet streams. As one of ordinary skill in the art can readily see, in some instances, the '506 patent teaches that volume of anti-solvent present must be greater than the volume of feed solution present. Yet in other instances, it teaches that the volume ratio be 1:1, and in other instances, even teaches that that the volume ratio be ***less than 1***. Moreover, the '506 patent teaches excess of anti-solvent be added to the stirred vessel ***after*** the

jets of medicament solution and anti-solvent have impinged upon each. Such teachings are in stark contrast to the teachings of the instant Application, i.e., that the volumetric ratio of anti-solvent to medicament solution is at least 2:1, and all the anti-solvent used is delivered via the anti-solvent jet stream. Hence, taken as a whole, the '506 patent does not teach or suggest the instant Invention, ***and even teaches away from it.*** MPEP § 2141.02 makes clear that

> [a] prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984)."

(Emphasis original).

In addition, none of the assertions the Examiner made in response to previously filed arguments provide any support for the Examiner's belief that the instant invention is obvious in light of the teachings of the '506 patent.

Firstly, it is difficult to see the relevance of assertion (a) in supporting this rejection. As the Examiner is well aware, every Tuesday the United States Patent and Trademark Office issues patents in fields in which patents have previously been issued. Thus, simply because the '506 patent and the instant Invention are in the same field of endeavor in no way makes or implies that the instant Invention is obvious.

Secondly, it is respectfully submitted the Examiner is incorrect in asserting that Applicants agree that the teachings of the '506 patent recognize the volume flow of feed and anti-solvent as an important factor in producing crystals having desired particle size. Applicants have made no such admission. Rather, Applicants have pointed out the Examiner the '506 patent teaches a range of volumetric ratios and flow rates. For example, Example 2 of the '506 patent teaches "the flow rate from each jet was 1.1 liter/min." Similarly, Examples 6 and 7 teach the

volume flow rate for the anti-solvent and the medicament solution are equal. In contrast though, Example 5 teaches that the flow rate of the feed solution was 2.6 times that of the anti-solvent[1].

Moreover, the '506 patent teaches that the flow rate is only important in order to ensure that a particular volumetric ratio of feed-solution to anti-solvent is obtained. Indeed, col. 6, lines 63-68 through col. 7, lines 1-2 of the '506 patent make clear:

> Each jet apparatus can be manipulated independently ***to attain the desired final fluid composition ratio***. When the desired flow ***ratio*** of one jet to the other differs from unity, preferably the difference is compensated for by appropriate sizing of entry tubes. For example, if a 4:1 volumetric ratio of feed solution to anti-solvent is desired, the entry tube delivering feed solution should be twice the diameter of the entry tube delivering anti-solvent.

Yet, for reasons discussed above, the '506 patent provides no teachings or suggestion that the volumetric ratio of anti-solvent to medicament solution always be 2:1 or greater. Indeed, in addition to other arguments set forth above, the passage recited immediately above further demonstrates that point. In the passage, a hypothetic ratio is used, i.e. "For example, if a 4:1 volumetric ratio of feed solution to anti-solvent is desired,...." Upon reading this sentence, it is reasonable to assume that, at some point of time, a person of ordinary skill in this art may want such a ratio in order to produce crystals of a medicament having a particular size. Yet, col. 8, lines 14-17 of the '506 patent teaches a 3:1 volumetric mixture of feed solution to anti-solvent produces crystals of Proscar® that are "...essentially the same as those from conventional batchwise crystallization, i.e., they require milling."

[1] Col. 9, lines 55-67 of the '506 patent states that the feed solution had a volume of 1400 ml and passed through a nozzle having a diameter of 1.0 mm, the anti-solvent had a volume of 538 ml and passed through a nozzle having a diameter of 0.5 mm, and both solutions passed through their respective nozzle in 1 minute, 45 seconds. Hence, since 1400 ml of feed solution passed through its nozzle in the same amount of time it took 538 ml of anti-solvent to pass through its nozzle, then the flow rate of feed solution is 2.6 times faster than that of the anti-solvent.

In stark contrast, the instant Invention clearly teaches that the ratio of the volume flow of anti-solvent to medicament solution exceeds 2:1. Page 8, lines 10-13 of the instant Application clearly explains:

> As described above ***an excess of anti-solvent is <u>needed</u> and the ratio of the flow rate of anti-solvent to medicament solution must be greater than 2:1***, preferably greater than 10:1, and even more preferably 15:1 and 30:1 (emphasis added).

Furthermore, as explained above, in responding to previously made arguments regarding the control of the velocity of jet streams, the Examiner has been inconsistent, and it is this very inconsistency that demonstrates that the instant Invention is unobvious in light of the teachings of the '506. In particular, on page 3 of the previously issued Office Action, the Examiner admitted that the '506 patent does not streams having velocities that exceed 30 m/s or 50 m/s. However, the Examiner asserted that the '506 patent suggests that a higher velocity is desirable for the method taught therein, and that any limitations on the upper limit of the velocity are only due to "practical difficulties". Hence, the Examiner believes the teachings of the '506 patent clearly suggest velocities higher than 25 m/s. There lies the inconsistency, i.e. it is unreasonable for the Examiner to assert velocity streams of the instant Invention are obvious in light of the teachings of the '506 when the Examiner has admitted the velocities of the '506 patent are limited to "practical difficulties", and Applicants teach overcoming such a practical difficulty, and recite such teachings in their Claims. Indeed, instant Application makes clear that, at velocities of 30 m/s or higher, velocities the Examiner has ***admitted*** are not taught in the '506 patent, ***Applicants discovered*** that in producing higher quality crystals:

> Any variation in velocity of either or both streams can cause a variation in psd [particle size distribution]. The cyclic variation which can be caused if pumps are used to generate the streams may be enough to produce the broad/double size distribution referred to

> above. ***In order to reduce this effect to acceptable levels*** anti pulsation devices may be required on the pumps. It has also been observed that cyclic variations in the velocity of either or both streams can lead to higher levels of residual solvent becoming entrapped in the crystal structure of the precipitated product.

(Page 5, lines 6-12 of the instant Specification (emphasis added)).

The passage of the instant Specification reproduced above makes clear that, when using higher velocities than those exemplified in the '506 patent to produce crystals of higher quality, such as 30 m/s, Applicants discovered a heretofore unknown "practical difficulty", namely a cyclic variation in velocity caused by pumps. In order to overcome this difficulty, and produce crystals of higher quality, Applicants used higher stream velocities than those disclosed in the '506 patent, and discovered that the velocity of the medicament solution stream and the velocity of the anti-solvent stream must be controlled to substantially remove cyclic variations. Indeed, such a limitation is set forth in claim 1.

The Examiner though has asserted the instant Invention is obvious in light of the teachings of the '506 patent because the Examiner believes the '506 patent suggests that a higher velocity is desirable for the method taught therein, and that any limitations on the upper limit of the velocity are only due to "practical difficulties". The Examiner cannot have it both ways. Consequently, since the Examiner has admitted the upper limit of the stream velocity is limited by "practical difficulties", and since the instant Invention teaches overcome such a practical difficult, it is respectfully submitted that, contrary to the Examiner's assertions, the '506 patent does not suggest velocities used in the instant Invention, i.e. beyond a "practical difficulty."

Finally, the Examiner has asserted that the pending Claims do not clearly recite the means for controlling variations in velocities. However, Applicants make clear in the instant

Application that an anti-pulsation device is sufficient for controlling variations in velocity. Moreover, it is respectfully submitted that one of ordinary skill can readily control variations in velocities using routine laboratory techniques.

Consequently, for the foregoing reasons, it is respectfully submitted Claims 1-30 are indeed ***unobvious*** to one of ordinary skill in the art in light of the teachings of the '506 patent, and this rejection should be withdrawn.

Furthermore, Claim 8 has been rejected under 35 U.S.C. § 103(a) as being patentable over the teachings of the '506 patent in view of the teachings of U.S. Patent 4,599,294 (the '294 patent). The Examiner's interpretations of the teachings of the '506 patent are discussed above. The Examiner has admitted though that the '506 patent does not specifically teach the use of the dimethylformamide as a solvent. However, the Examiner believes that the '506 patent teaches that the list of solvents disclosed therein and discussed above is not exhaustive. Hence, the Examiner is of the opinion that the DMF is a known solvent in the pharmaceutical art. In support of this opinion, the Examiner has relied upon the teachings at col. 10, lines 42-57 of the '294 patent, where a large list of solvents is found, including solvents such as DMF, methylene Chloride, and ethyl acetate. It is the position of the Examiner that one of ordinary skill in the art would have been motivated to use any known solvent in the teachings of the '506 patent to achieve the desired purpose, particularly because of the statement in the '506 patent that the list of solvents set forth therein is not exhaustive. Moreover, the Examiner believes the selection of a material based upon its suitability for its intended use is obvious absent a clear showing of unexpected results attributable to the Applicant's specific selection. Hence, it is the Examiner's position that the instant Invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the instant Invention was made.

Furthermore, the Examiner has asserted that previous arguments made to the Examiner regarding this rejection are not persuasive. One previously made argument, i.e. that Claim 8 is unobvious because it depends from Claim 1, which Applicants believe is unobvious in light of the teachings of the '506 patent, was not found persuasive because the Examiner has asserted Claim 1 of the instant Application is obvious to a skilled artisan in light of the teachings of the '506 patent.

The Examiner has also disagreed with the previously made argument that the '294 is not analogous art to the '506 patent, and consequently cannot be combined with the '506 patent. In particular, the Examiner has asserted that the teachings of the '294 patent are directed towards producing particles, and dimethylformamide is recognized as one of the solvents. Moreover, the Examiner has asserted that the instant Claims do not specify a particular medicament or drug type, and thus, in the Examiner's opinion, are broad. Hence, it is the Examiner's position that the combination of the teachings of the '506 patent and the teachings of the '294 patent is proper.

This rejection is respectfully traversed. Applicants respectfully reiterate to the Examiner that a skilled artisan would not be motivated to combine the teachings of the '506 patent with the teachings of the '294 patent. As explained above, the '506 patent teaches, *inter alia*, a process for the crystallization of an organic ***pharmaceutical compound*** by contacting one or more jet streams of a feed solution of the organic pharmaceutical compound with one or more jet stream of an anti-solvent. In stark contrast, the '294 patent discloses, *inter alia*, a method of producing ***a dry spherical toner for printing***, wherein the method utilizes ***electrostatic force*** (see claim 1 of the '294 patent). MPEP § 2141.02 clearly states that in order for the Examiner to rely on a reference under 35 U.S.C. § 103, the reference must be ***analogous*** prior art. The Court of Appeals for the Federal Circuit has also explained, "In order to rely on a reference as a basis for

rejection of an applicant's invention, the reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned." *In re Oetiker*, 977 F.2d 1443,1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992).

Since the teachings of the '294 patent clearly are not in the field of the instant Invention and the '506 patent (circular toner as opposed to a therapeutic agent), and are not reasonably pertinent to the particular problems with which both the '506 patent and the instant Invention are concerned, it is respectfully submitted that the '294 patent is directed to non-analogous art, and can not be relied upon in making this rejection. Thus, for all of the foregoing reasons, this rejection should be withdrawn.

Also, Claims 10 and 28 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over the teachings of the '506 patent in view of the teachings of U.S. Patent 3,897,779 (the '779 patent). The Examiner's interpretations of the teachings of the '506 patent are discussed above. The Examiner has admitted the '506 patent does not teach the use of the active agent triamcinolone acetonitride. However, the Examiner believes the '506 patent teaches that many active agents can be used. With respect to the '779 patent, the Examiner has asserted this patent teaches that triamcinolone acetonide is used in inhalation therapy, where high surface area, small particles, and improved stability and purity are greatly desired. Hence, it is the Examiner's opinion that triamcinolone acetonide would be an excellent medicament for the invention disclosed in the '506 patent. Moreover, the Examiner believes that, absent a showing of unexpected results, the use of a particular active agent in a known process does not impart patentability. Hence, in the opinion of the Examiner, the instant Invention as a whole would

have been *prima facie* obvious to one of ordinary skill in the art at the time the instant Invention was made.

Furthermore, the Examiner has not found arguments previously made regarding this rejection persuasive. In particular, the Examiner has asserted that that the '779 patent teaches the claimed drug as having high surface area and small particles, which the Examiner believes the desired under the teachings of the '506 patent to achieve improved stability and purity. Moreover, the Examiner believes that both the '506 and '779 patents are directed towards drug formulations having small particles of drug and thus are analogous in nature. Hence, it is the Examiner's position that this combination of references is proper and one of ordinary skill in the art would have included the triaminicolone of the '779 patent in the method of producing drug particles set forth in the '506 patent, with an expectation of producing small particles having high bioavailability, which is also desired by the '779 patent.

This rejection is respectfully traversed. Claim 10 is dependent upon Claim 1, and Claim 28 is dependent upon Claim 29. For reasons set forth above, Claims 1 and 19 are unobvious in light of the teachings of the '506 patent. The '779 patent teaches a method of treating asthma which "...is based on the discovery that the discharge from an aerosol container having therein a suspension of triamcinolone acetonide in a propellant can be suspended in a dry vaporized propellant mixed with air by the use of a deceleration chamber...." (Col. 1, lines 22-26 of the '779 patent). Thus, the '779 patent teaches ***nothing*** with respect to crystallizing a therapeutic compound.

Moreover, Claim 1 of the instant Application is directed towards, *inter alia*, "[a] method of producing medicament particles comprising dissolving the medicament in a solvent, producing one or more streams of medicament solution and contacting these streams with one or

more streams of anti-solvent in order to produce a region of turbulent mixing in which rapid precipitation of medicament ***crystals*** takes place..." (emphasis added). However, in col. 8, lines 50-54 of the '779 patent, it is explained that:

> Triamcinolone acetonide was ***micronized*** in a fluid energy mill until 90% by weight was in the particle size range of 1 to 5 microns (emphasis added).

It is respectfully submitted that micronizing a crystal in a fluid energy mill produces amorphous particles. Yet, as explained above, the instant invention is directed towards, *inter alia*, producing medicament ***crystals***.

For the foregoing reasons, it is respectfully submitted that ***no*** motivation or suggestion exists in either the '506 or '779 patents to combine them as the Examiner has done in making this rejection. Hence, Claims 10 and 28 are unobvious to one of ordinary skill in the art in light of this combination references, and this rejection should be withdrawn.

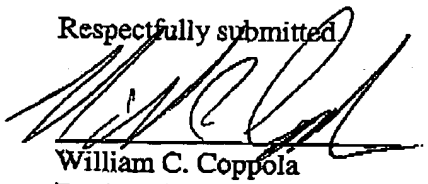
Fees

No fees are believed to be necessitated by the instant response. However, should this be in error, authorization is hereby given to charge Deposit Account no. 18-1982 for any underpayment, or to credit any overpayments.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of the instant Application. The Claims as amended are believed to be in condition for allowance, and reconsideration and withdrawal of all of the outstanding rejections is therefore believed in order. Early and favorable action on the claims is earnestly solicited.

Respectfully submitted,



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